Cancer Research

Cancer Research, Vol 53, Issue 4 819-825, Copyright © 1993 by American Association for Cancer Research

ARTICLES

Pseudomonas exotoxin-based immunotoxins containing the antibody LL2 or LL2-Fab' induce regression of subcutaneous human B-cell lymphoma in mice

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We have produced immunotoxins using LL2, a monoclonal antibody which binds to human B-cell lymphomas and which, in a radioiodinated form, induced responses in lymphoma patients (D.M. Goldberg et al., J. Clin. Oncol., 9: 548-564, 1991). We have coupled LL2 to Lys-PE38KDEL, a derivative of Pseudomonas exotoxin (PE) which does not bind to the PE receptor. LL2-PE38KDEL was cytotoxic toward several Burkitt's lymphoma lines, with 50% inhibitory concentration values ranging from 2 to 6 ng/ml (10-30 pM). Another immunotoxin, LL2-Fab'-PE38KDEL, was produced by chemically coupling the Fab' fragment of LL2 to Lys-PE38KDEL. LL2-Fab'-PE38KDEL also was cytotoxic toward the Burkitt's cells, with a 50% inhibitory concentration of 1-2 ng/ml (13-24 PM). The antibody LL2 alone had no cytotoxicity toward the malignant cells, and excess LL2 prevented the cytotoxicity of LL2-PE38KDEL and LL2-Fab'-PE38KDEL. Control immunotoxins UPC-10-PE38KDEL and Mu-9-Fab'-PE38KDEL were not cytotoxic. LL2-PE38KDEL and LL2-Fab'-PE38KDEL bound to cells with 50% and 17% of the affinity of LL2, respectively. Both immunotoxins, but not UPC-10-PE38KDEL, prevented the development of CA-46 tumors in nude mice. LL2-PE38KDEL and LL2-Fab'-PE38KDEL, but not the control immunotoxins, led to complete regressions of measurable s.c. CA-46 tumors in nude mice, when given at 50% and 35% of the 50% lethal dose, respectively. LL2 alone significantly retarded the growth of CA-46 tumors but did not cause complete tumor regressions. Immunotoxins containing derivatives of Pseudomonas exotoxin can be targeted to human B-cell lymphoma and merit further study as potential therapeutic agents.

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